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SUBJECT OF INVESTIGATION

STUDIES OF RESPIRATORY DISEASES
DUE TO
AIR POLLUTION
IN
THE TOKYO-YOKOHAMA AREA

RESPONSIBLE INVESTIGATOR

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Among 237 cases of asthmatic patients at our clinic there were only 15 cases who developed their 1st asthma in T-Y area after their move to this industrialized area from rural areas but none of them presented compatible characteristics with the entity of the so-called T-Y asthma, though some presented quite similar pictures. (Author).

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Abstract

To investigate air pollution respiratory diseases (especially T-Y asthma) among Japanese, mass survey in the Niigata area and T-Y area was carried out. Subjects submitted for statistic analysis were 2825 in total. There were increased incidence of respiratory symptoms such as chronic coughing, increased sputum production and throat irritation among the subjects who are living in T-Y area. This incidence was highest in the native group of T-Y area and particularly high among smokers and subjects with allergic constitution. There were no increased incidence of air way obstructive diseases in T-Y area but group of subjects who were exposed to heavy air pollution tended to have low vital capacity. These results give the evidence that air pollution is harmful for respiratory tract.

There were no definite evidence that respiratory sensitivity to inhaled acetylcholine in subjects in T-Y area was increased, inspite of the fact that asthmatic patients have significantly high sensitivity to acetylcholine. On the other hand, 7 cases of T-Y asthma at Zama U.S.Army Hospital showed the range of bronchial asthma and chronic bronchitis.

Among 237 cases of asthmatic patients at our clinic there were only 15 cases who developed their 1st onset of asthma in T-Y area after their move to this industrialized area from rural areas but none of them presented comparable characteristics with the entity of the so-called T-Y asthma, though some presented quite similar pictures.

Studies Of Respiratory Diseases Due To Air Pollution In The Tokyo-Yokohama Area

Environmental atmospheric conditions have been considered as important contributing factors in the pathogenesis of respiratory diseases by many authors(1-11). Since the report of Tokyo-Yokohama asthma in 1954(1), the name has become quite popular among U.S. Military personnel, assuming air pollution in this particular area as a contributing factor. Nevertheless, the existence of such specific respiratory ailment among Japanese people has been questioned by most Japanese physicians, though admitting that air pollution is harmful to the respiratory system as reported by many authors(2-4). It should be noted that the Tokyo-Yokohama area (T-Y area) is an industrialized area, fronting on a bay and enclosed by hills and bluffs, providing an ideal condition for smog formation and retention, and air pollution has lately become a great industrial as well as a medical problem. Consequently, the aim of our study is to investigate how highly and in what incidences respiratory system has been effected by air pollution in T-Y area, and to explore the possibility of existence of T-Y asthma among the Japanese population.

Therefore a comparative mass survey in two areas, namely Niigata and T-Y areas, were carried out and asthmatic subjects who visited our clinic were studied to find a case of the so-called T-Y asthma among them.

Material and Method

Mass Survey:

Worker in the branch factories of an oil company and a casting factory were chosen for this study. The factories of this oil company were located in Kashiwazaki, Niigata, Yokohama, and Kawasaki. Kashiwazaki and Niigata (Niigata area) are situated more than one hundred and fifty miles from Tokyo, beyond the Kanto plain and facing the Japan Sea, and their population is about 130,000 and 330,000 respectively (Fig. 1). Because this area is not industrialized and because the type of work and environmental condition in the factories in both areas are similar it was thought to be a good control. Many workers (approximately 34%) other than the natives of T-Y area in the Yokohama and Kawasaki factories in this particular oil company are from the Niigata area for the following historical reasons: oil was first found in the Niigata plain in Japan and the first oil factory in Japan was constructed in Kashiwazaki. The factories in Yokohama and Kawasaki are located in the industrialized area. The casting factory is located in the center of the most smoky industrialized area of Kawasaki and this is the reason why this company was selected as the subject.

Questionnaires including age, height, weight, birthplace, present address, length of stay in T-Y area, family history of asthma and allergy, past history, smoking habit, chronic respiratory symptoms such as sputum production, throat irritation, coughing and shortness of breath, effect of change in place of residence upon respiratory symptoms etc. were handed to each subject prior to routine physical and roentgenologic examinations and pulmonary function test with an accompanying instruction sheet and explanation on how to fill in the questionnaire. On the day of examination, each subject was asked the same questions to check the accuracy of their answers.

Forced expiratory volume (FEV) was determined with 13.5 liter Benedict-Roth respirometer using 1920 mm per minute drum speed with each subject to find air way obstructive changes.

Chest X-rays were reviewed and subjects (approximately 10% of total cases) with previous chest operations, injuries and organic pulmonary diseases considered due to causes other than air pollution were excluded.

In addition, those who have moved from T-Y area to rural areas or vice versa more than once were excluded to make statistic analysis simpler.

Female subjects were also excluded from the statistic analysis mainly because their number were few and because the majority of cases find it difficult to perform forced expiration. Subsequently, the subjects numbered 473 in the Niigata-area and 1463 in T-Y area in the case of the oil company, and 889 in the case of the casting company in Kawasaki. Their age ranged from 15 to 58.

Subjects in T-Y area were divided into 2 major groups. Subjects who were born and raised in T-Y area were classified as the native group and subjects who were born in areas other than T-Y area and moved into T-Y area as the non-native group. This group was further divided into 3 groups, namely, subjects who had been in the area less than 5 years were called group I, subjects living there for from 5 to 10 years group II, and subjects living there over 10 years group III.

These groups were compared with each other. Since the casting factory presents special characteristics in the point of difference in the type of work and high incidence of pneumoconiosis due to metal dust (25%), the oil factories and casting factory groups were compared separately but subjects in the Niigata area were used as control in both groups.

Respiratory symptoms were compared between the Niigata area and T-Y area, as a whole and also from the aspect of smoking habit and allergic constitution. Ratio of the actual vital capacity to normal predicted value for Japanese male for his age and height was calculated in each subject and the mean values were compared in each age group by t-test. Integrated probability curves were drawn to see the deviation of vital capacity in each group. Also, the values of $FEV_1/FEV_0 \times 100$ were compared in each age group.

In the Kawasaki factory of the oil company 500 ug of acetylcholine was inhaled by 140 subjects, 1000 ug by 517 subjects, and 2000 ug by 146 subjects. FEV_1 was determined before and 5 minutes after acetylcholine inhalation to see air way obstructive changes. When FEV_1 decreased more than 10 per cent, it was considered to be positive.

The study was carried out between Oct. 1, 1962, and Dec. 20, 1962, the period when incidence of bronchial asthma used to be in the highest in the year.

Investigation to find a case of T-Y asthma from asthmatic patients at our clinic:

Charts of 237 cases of asthmatic patients at our clinic were carefully reviewed to find a typical case of the so-called T-Y asthma[5-7] which is characterized by the following points: the onset of asthma starts after moving into T-Y area; hardly no significant response to bronchodilator; marked response after separation from T-Y area in the early stages; quite rapid regression of respiratory capacity toward severe emphysema, etc. Their age ranged from 6 to 65 years of age. Some of them were subjected to CO diffusion study by single breath technique. Two of them initiated their asthmatic attacks after moving into T-Y area and they have quite similar history with the so-called T-Y asthma.

An aqueous solution of acetylcholine was prepared in double fold dilutions starting at 100,000 ug/cc down to 6 ug/cc. Starting at the weakest strength and gradually increasing, 0.5 cc of acetylcholine solution was inhaled by the subject until FEV_1 decreased by more than 15 per cent of original FEV_1. The amount of acetylcholine at this point was regarded as the threshold of respiratory tract to acetylcholine. In order to see the acetylcholine threshold in various respiratory diseases, the study was performed on 99 cases of asthmatic patients, 6 cases of chronic bronchitis (only chronic cough and no paroxysmal attack of wheezing and shortness of breath), 7 cases of heavy smokers (more than 30 cigaretts a day and more than 300 smoking year) and 20 cases of normal subjects. Same study was also carried out in 7 cases of the so-called T-Y asthma at U.S. Zama Army Hospital located in Zama, Japan with the cooperation of Lt. Col. Phelens and Maj. Spetnitz.

Result.

Mass survey: Number of subjects, mean value of age, incidence of smokers, mean smoking years, etc. are listed in Table 1. There were increased incidences of shortness of breath, chronic throat irritation, coughing and sputum production among the native group of T-Y area and non-native group in comparison with the Niigata area (Tables 2, 3). This became more apparent with advanced age groups and especially marked in older age group of natives in T-Y area. When each group was subdivided into smoking and non-smoking groups and also into groups with allergic constitution (including allergic family history) and with non-allergic, these incidences were higher in the smoking group and in the allergic group (Tables 2, 3).

In comparison of mean values of ratio of vital capacity to normal predicted value in each age group, there were no significant difference in each age group except in older age groups where vital capacity tended to be lower in the T-Y area groups than the native group of Niigata area. Subjects of casting company generally showed lower value of vital capacity than the native oil factories group in the Niigata area (Table 4). This fact was clearly shown by integrated probability curve (Figure 2). Ratio between one second forced expiratory volume (FEV_1) and total forced expiratory volume (FEV_0) was classified in each group as shown in Table 5.

As the value between 78 and 83 of $FEV_1/FEV_0 \times 100$ were occasionally observed in the subjects whose vital capacity were far above 5,000 cc, it was thought to be more reasonable to consider air way obstructive changes when $FEV_1/FEV_0 \times 100$ was less than 78 in some cases. It was, however, arbitrarily

but 80% as to be the border of normal range in this report.

FEV_1/FEV_0 showed progressive decrease with advancing age and this trend was quite apparent in the native group of T-Y area (Figure 3).

Incidences of subjects with respiratory symptoms were quite high among the subjects with reduced FEV_1/FEV_0 but there were considerable number of subjects with reduced FEV_1/FEV_0 but without any respiratory symptoms (Table 6).

In the acetylcholine inhalation study, 2 out of 140 subjects (1.4%) showed a significant reduction of FEV_1, after 500 ug of acetylcholine inhalation, 18 out of 517 (3.5%) after 1,000 ug and 5 out of 146 (3.4%) after 2,000 ug. Out of these 25 cases, 5 had subjective symptoms related to the chronic respiratory diseases such as chronic coughing, throat irritation, increased sputum production and shortness of breath. Nine had bronchial asthma or urticaria in the past (Table 7).

Study at our clinic:

Bronchial threshold to acetylcholine of almost all of the asthmatic patients were below 1563 ug mostly below 390 ug (Figure 4). In normal subjects, it was much higher, though most of them developed irritation of throat and coughing. Chronic bronchitis ranged between asthmatic patients and normal subjects, and heavy smokers were mostly identical with normal subjects. The 7 cases of T-Y asthma came in the same range as chronic bronchitis and bronchial asthma.

There were only 15 cases which had developed their symptoms within the past 15 years definitely after their move to T-Y area, among 237 asthmatic patients who visited our clinic in the past two years, three out of those 15 cases showed positive provocative test with inhalation of allergen (house dust extract in this study), 8 showed good response to bronchodilator, 2 presented increased blood eosinophile and 2 showed no significant improvement after moving out from T-Y area (Table 8). CO diffusion were mostly within normal range in asthmatic patients including 2 cases whose asthmatic symptoms started shortly after their move to T-Y area.

Case report: Case 1. (Table 9)

The 1st case is a 28-year-old Japanese male who was born in Kagoshima. At the end of January 1960, he came to Tokyo. He was perfectly well until Sept., 1960, at which time he developed consistent coughing in the night and early morning -- especially at the time of getting up. No sputum production, no dyspnoea, no rhinorrhea at that time. This coughing gradually subsided in 2 to 3 weeks and he was apparently well until May 1961, when he developed coughing as before. This time, he had rhinorrhea and also noted mild wheezing occasionally and shortness of breath twice in the night but all of these symptoms were not severe enough to seek medical attention and subsided within few weeks. At the end of September, he developed the same symptoms but to a severer degree. He suffered shortness of breath and diagnosis of bronchial asthma was made. He was treated with bronchodilator, antibiotic, steroid, etc., but his response was not

quite satisfactory and visited our clinic. He had no previous history of asthma or allergy. Family history did not reveal any allergy either. Laboratory studies showed that WBC was 7,750 with 14% of eosinophil. Skin test was positive to house dust extract, etc.. Inhalative provocation test of house dust was strongly positive.

He was treated with house dust hyposensitization, steroids, antibiotics and various bronchodilators but his response was not quite satisfactory though able to get temporary relief by inhalation of bronchodilator or intravenous aminophylline injection. Since fall of 1961, he had almost constant wheezing and shortness of breath aggravated by attack. His asthmatic condition was worse between September and March, especially during night and early morning. In January 1963, he moved from T-Y area and went to Kagoshima, his native land, according to our recommendation and stayed there for 3 months but he came back and stated that his condition was about the same in Kagoshima. Shortly after he came back, he developed spontaneous pneumathorax from which he recovered uneventfully in a few weeks. During that time, he stated that he felt fairly well.

Case 2. (Table 7)

A 29-year-old Japanese male who was born in Sakhalin moved to the Japanese homeland after the war. In 1955 he came to Tokyo and moved to Kawasaki in 1957. He was perfectly well until May of 1961 when he developed a hacking cough which lasted for 1 week followed by tightness of chest. He was hospitalized for 3 weeks from June 1st. These symptoms recurred in the fall with a severer degree of dyspnoea. He was hospitalized for 2 months (October and November). During that time, his symptoms were worse between 10 o'clock at night and 5 o'clock in the morning. He was referred to our clinic shortly after his discharge. He had no family history of allergy. All allergic skin tests were negative. He responded to ordinary oral and inhalative bronchodilator fairly well. He was treated with aurothioglucose (Solganal B) injection in addition to steroids and to ordinary antiasthmatic drugs. His response was satisfactory and no medication was needed after few months except occasional incidences when he takes oral bronchodilators but no steroids. Aurothioglucose injection was kept weekly until 40 injections were completed and he is now taking it once in 3 weeks. In the meantime he moved out from T-Y area for business reasons and was apparently well. In March 1963, he came to Kawasaki to visit our clinic and experienced rather severe asthmatic attack early the next morning which was controlled by bronchodilator. He stated that it was an attack few months free from asthma. He stayed there two more days but without any more recurrence of symptoms.

Case 3. (Table 7)

A 19 year old female who was born in Tokyo, moved to Fukui at the age of 2 and came back to Tokyo at the age of 13. She was apparently well until age of 15, when she was working in pharmaceutical company and experienced an acute onset of shortness of breath right after she smelled pyridin odor which spreaded by the damage of an gas exhauster. For few

months after this episode, she experienced shortness of breath whenever she was exposed to pyridin odor. In January 1962, she developed rather severe status asthmatics following cold. Since that time she has had rather frequent attack of shortness of breath and wheezing. She was referred to our clinic in January 1963. There were no family history of allergy or asthma. Her skin tests for various antigen were entirely negative. Blood counts and sputum examination were non contributory.

Discussion

There have been considerable number of reports concerning unfavorable effect of air pollutants (including physical and chemical) upon respiratory sy system[8-11]. Increased incidences of subjective respiratory symptoms in T-Y area can be caused not only by air pollutants in this particular industrial area, but many other possible causes, such as different climate, nutrition, housing condition, economical situation, etc. have to be considered. It seems, however, most plausible to conclude that these symptoms were mainly due to industrial air pollutants as the main differences between the two areas which affect respiratory system seems to be industrial air pollution. It is quite interesting to note that such respiratory systems were more predominant among the subjects with smoking habit and the subjects with allergic constitution. This is, in a way, in keeping with the finding at Zama Army Hospital where they stated that the so-called T-Y asthma was particularly observed among heavy-smokers.

From Table 4 and Fig. 2, it is apparent that when subject stayed in T-Y area long enough, their vital capacity tends to become lower and this is clearly observed in the casting company where cases of pneumoconiosis have been observed. Incidences of decreased FEV_1/FEV_0 (less than 80%) were higher in older native groups of T-Y area but no such tendency was seen in non-native groups in comparison with the Niigata groups. Incidences of respiratory symptoms are higher in reduced FEV_1/FEV_0 group. From these results it can be concluded that polluted air is harmful for respiratory system not only as the cause of respiratory symptoms but also as the cause of reduction of vital capacity. In spite of the possibility of existence of the so-called T-Y asthma among Japanese, however, we failed to find even a single case whose symptoms are compatible with it in this mass survey.

Among 237 asthmatic patients who visited our clinic, only 15 cases developed their onset of asthma in the past 15 years after their move to T-Y area. Some of them presented a generally similar picture with the so-called T-Y asthma but they have certain different characteristics as shown in Table 8. In other words, some of them showed obvious allergic basis for their asthma, some of them responded to bronchodilator quite well, some experienced no significant improvement even when they moved from T-Y area. The three cases reported as examples presented certain similarity with T-Y asthma but exhibited considerable differences. For instance, inhalation of house dust extract did provoke severe asthmatic attack in Case 1. Therefore it is quite certain that one of the major causes of his asthma is house dust, though there could very well be other causes of his asthma, Case 2 responded to bronchodilator quite well.

Because of the limited number of cases studied in our mass survey and as thmatic patients in our clinic, we can not make a definite statement. It is, however, quite obvious that the incidence of a typical case of so-called T-Y asthma among Japanese would be extremely low as to be almost non-existent. We are, however, not trying to state that air pollution has nothing to do with bronchial asthma. There have been already many reports confirming that air pollution has harmful effects upon bronchial asthma and we ourselves observed some cases whose first attack were provoked by strong chemical odors (Case 3) and also a considerable number of asthmatic patients whose respiratory symptoms were aggravated by smoke, fumes, or chemical odors, or simply by moving into T-Y area. On the other hand, some asthmatic patients felt better, though only for a short period of time, when moved to T-Y area from rural areas. It is conceivable that some cases could have never developed asthmatic conditions if they were living out of T-Y area but it is hard for us to conceive that air pollution will produce asthmatic attack in a short period in the subjects who had no constitutional disposition or no hypersensitivity of bronchial tree. We currently observed that we made guinea pigs inhale 50 - 100 p.p.m. of SO_2 for 30 minutes every other day for 7 times, the respiratory tract became more sensitive to acetylcholine observed by bodypletysmography. And low concentration of acetylcholine inhalation produced respiratory distress to the guinea pigs easily. This became more obvious right after inhalation of SO_2 (Fig. 5). In these animal experiments, exceedingly high concentration of SO_2 was used. Therefore it may not be feasible to apply this experimental result to human beings as it is. From this result, however, it is theoretically possible for them to have decreased acetylcholine threshold of respiratory tract when the subjects were exposed to heavily polluted air, though this seemed to be not the case in cigarette smoking.

From acetylcholine inhalation study of 803 subjects in Kawasaki, it was noted that there are a few subjects whose respiratory tracts are more sensitive than most of normal subjects even without having respiratory symptoms. It is not quite certain, however, whether they are sensitive to acetylcholine as the result of respiratory damage due to air pollution in T-Y area or as the result of allergic hypersensitization. There is also another possibility that they are congenitally hypersensitive to acetylcholine. Unfortunately we did not carry out the same study in rural areas and we can not go beyond this postulation at this time. Anyhow we are postulating that such subjects could be the one who would develop clinical respiratory symptoms, especially identical with asthmatic symptoms, in the future, if they are exposed long enough to chemical or physical air pollution.

Furthermore, if they are congenitally sensitive to acetylcholine they could be the one who would eventually develop bronchial asthma due to any cause such as allergens or chemical, physical and mechanical irritation to respiratory tract. However, still we can not ignore the possibility of potent allergen in T-Y area to which subjects were already sensitized prior to their move to T-Y area.

There seemed to be a considerable number of T-Y asthma cases among U.S. Army personnel but probably exceedingly low among Japanese. It is hard to realize why such a difference exists between Japanese and U.S. Army

personnel or foreigners coming to Japan. The possibility that their respiratory tract could be move sensitive than Japanese' constitutionally is quite unlikely since incidence of bronchial asthma shows no significant difference throughout the world.(12-14)

At the present time, we rather think that they probably tended to exaggerate and extended the scope of T-Y asthma and included in it many respiratory ailments with throat irritation, chronic coughing, wheezing or shortness of breath, even if they were just chronic common cold or respiratory infection and this is probably one of the reasons which made the incidence of T-Y asthma among U.S. personnel so high. It is true that the incidence of bronchial asthma rises sharply in fall and winter in Japan and it is also true that the degree of industrial air pollution is higher during those two seasons, but it should be emphasized that this observation alone does not necessarily produce the conclusion that bronchial asthma in T-Y area is particularly closely related to industrial air pollution, because the increase in bronchial asthma incidence in these seasons was observed in Japan for many years far before air pollution became a problem.

From our present study, it seems to be reasonable to state that the name of T-Y asthma is not quite feasible for Japanese people since the incidence of such respiratory ailment is almost non-existent and the incidence of bronchial asthma does not seem to have increased in particular in T-Y area though incidences of respiratory symptoms are much higher in T-Y area than in the rural areas.

Summary and Conclusion

To investigate air pollution respiratory diseases (especially T-Y asthma) among Japanese, mass survey in the Niigata area and T-Y area was carried out. Subjects submitted for statistic analysis were 2825 in total. There were increased incidence of respiratory symptoms such as chronic coughing, increased sputum production and throat irritation among the subjects who are living in T-Y area. This incidence was highest in the native group of T-Y area and particularly high among smokers and subjects with allergic constitution. There were no increased incidence of air way obstructive diseases in T-Y area but group of subjects who were exposed to heavy air pollution tended to have low vital capacity. These results give the evidence that air pollution is harmful for respiratory tract.

There were no definite evidence that respiratory sensitivity to inhaled acetylcholine in subjects in T-Y area was increased, inspite of the fact that asthmatic patients have significantly high sensitivity to acetylcholine. On the other hand, 7 cases of T-Y asthma at Zama U.S. Army Hospital showed the range of bronchial asthma and chronic bronchitis.

Among 237 cases of asthmatic patients at our clinic there were only 15 cases who developed their 1st onset of asthma in T-Y area after their move to this industrialized area from rural areas but none of them presented compatible characteristics with the entity of the so-called T-Y asthma, though some presented quite similar pictures. From our study, it may not be quite

feasible to use the name of T-Y asthma for Japanese since the incidence of air way obstructive diseases does not seem to have particularly increased in T-Y area. Possible reasons for the difference between our views and those of the U.S. military physicians were discussed.

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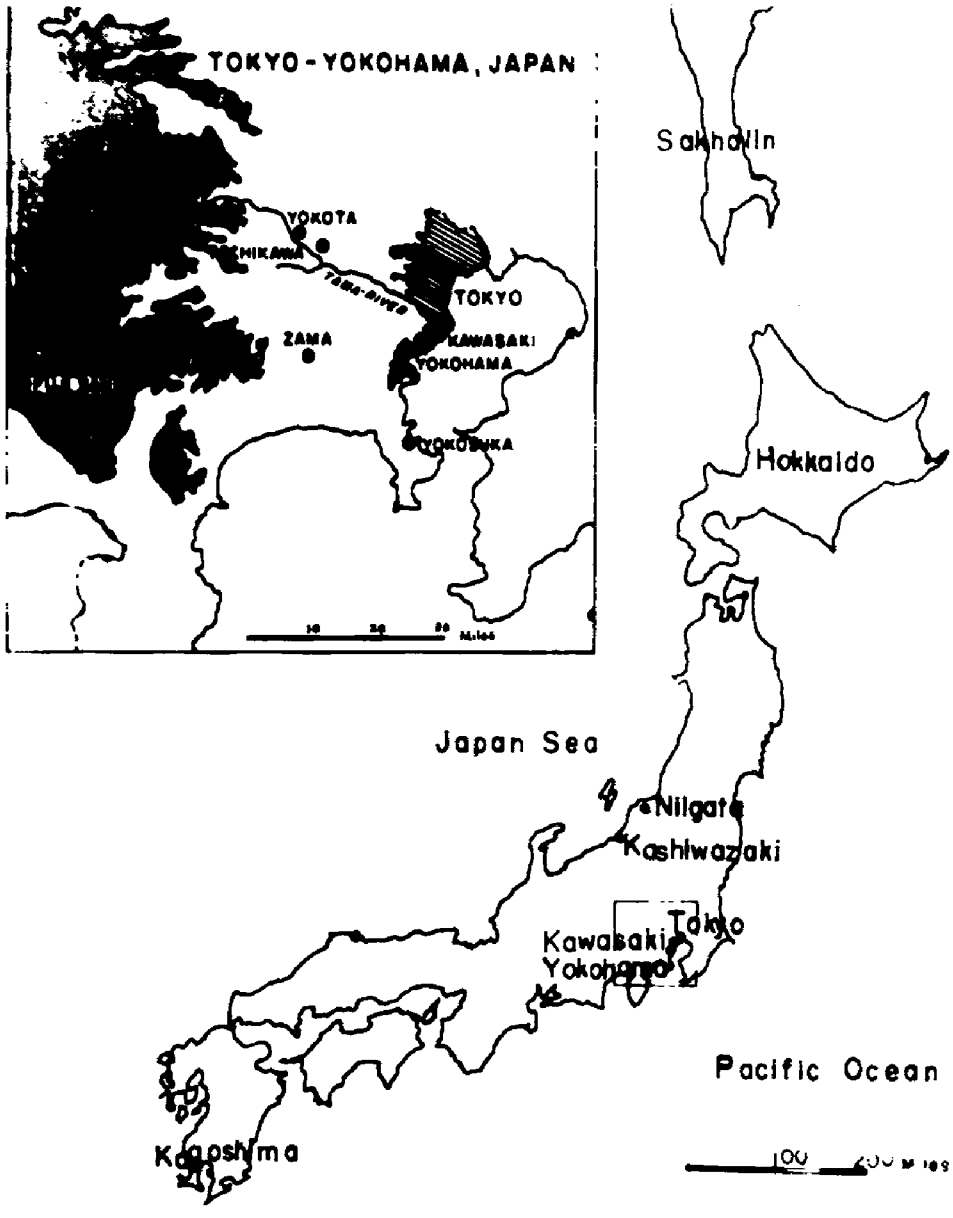

Fig. 1. Geographic Localization of Tokyo-Yokohama Area and Niigata Area

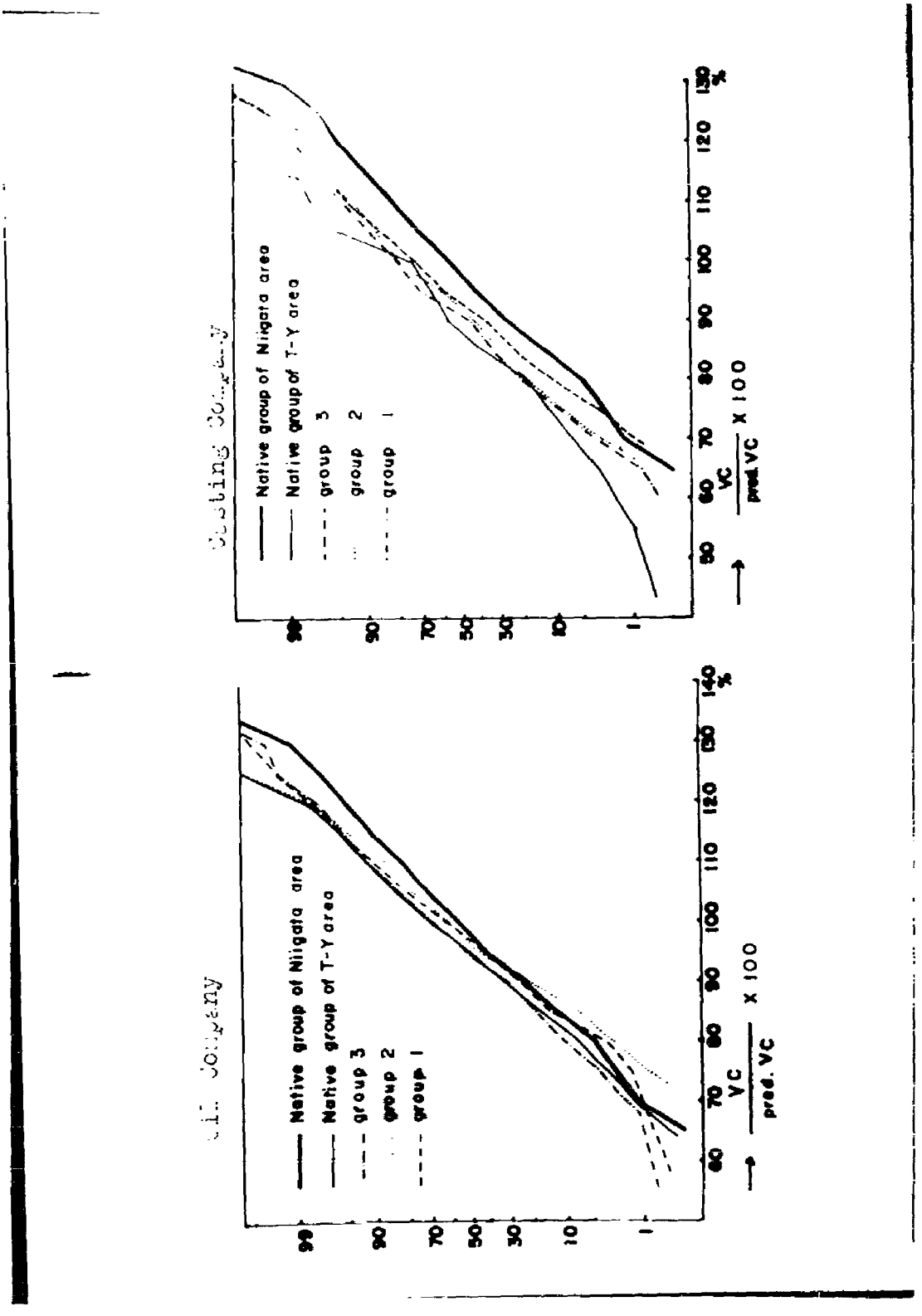

Fig. 2. Integrated Probability Curves of VC/pred.VC x 100 in Each Group.

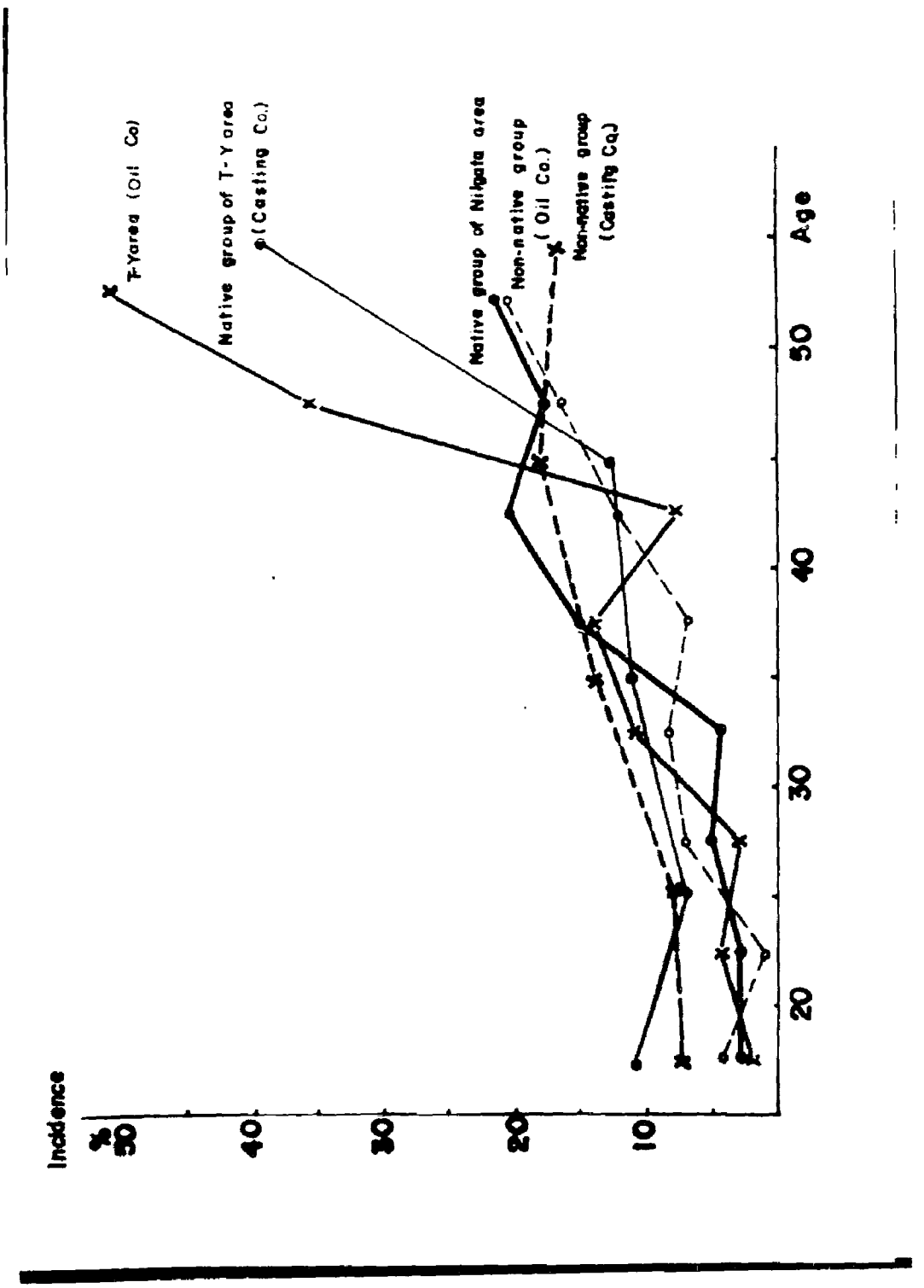

Fig. 3. Incidences of Subjects Whose FEV_1/FEV_0 x 100 were less than 80 in Each Group.

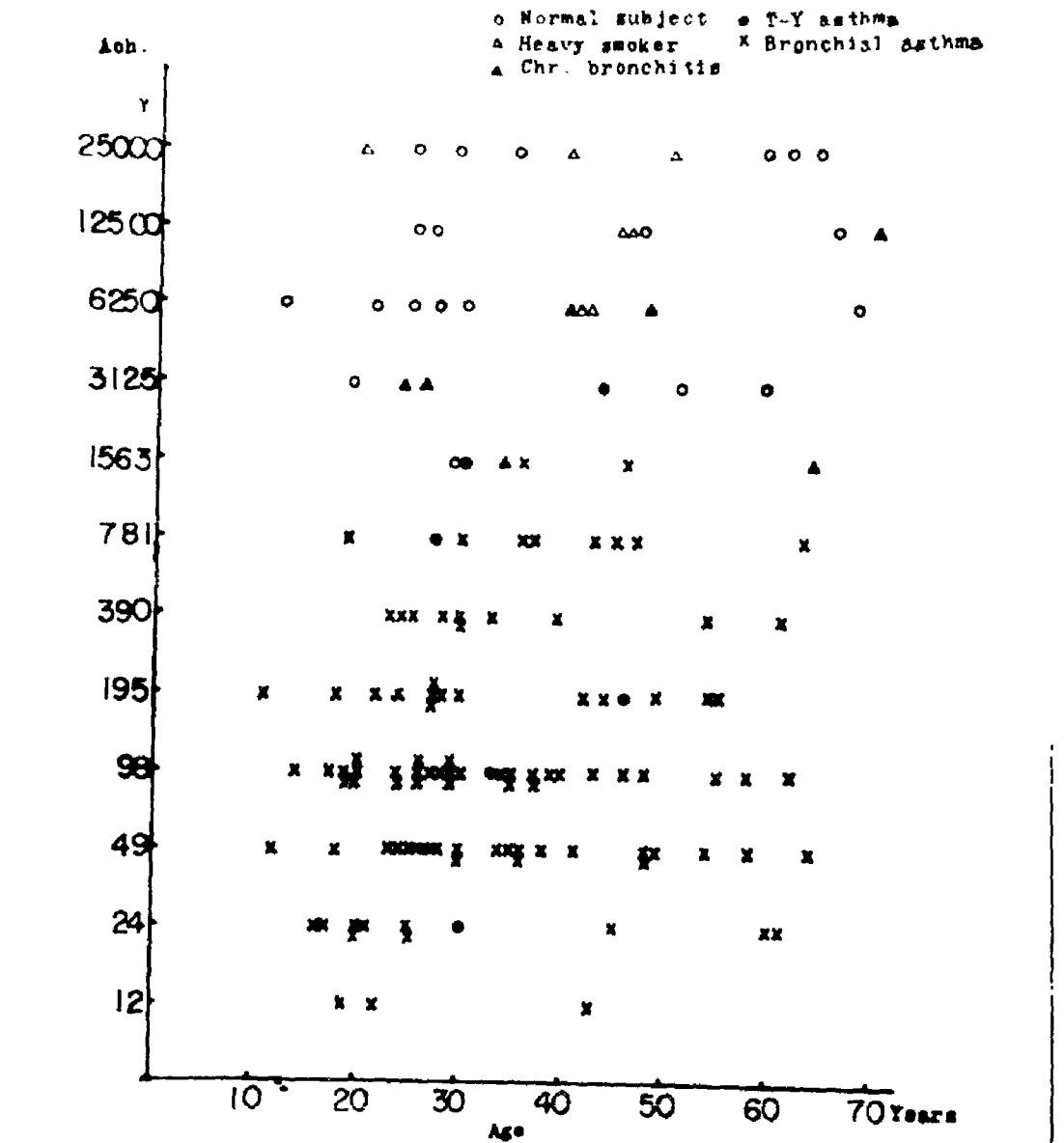

Fig. 4. Bronchial Threshold to Acetycholine in Various Respiratory Diseases.

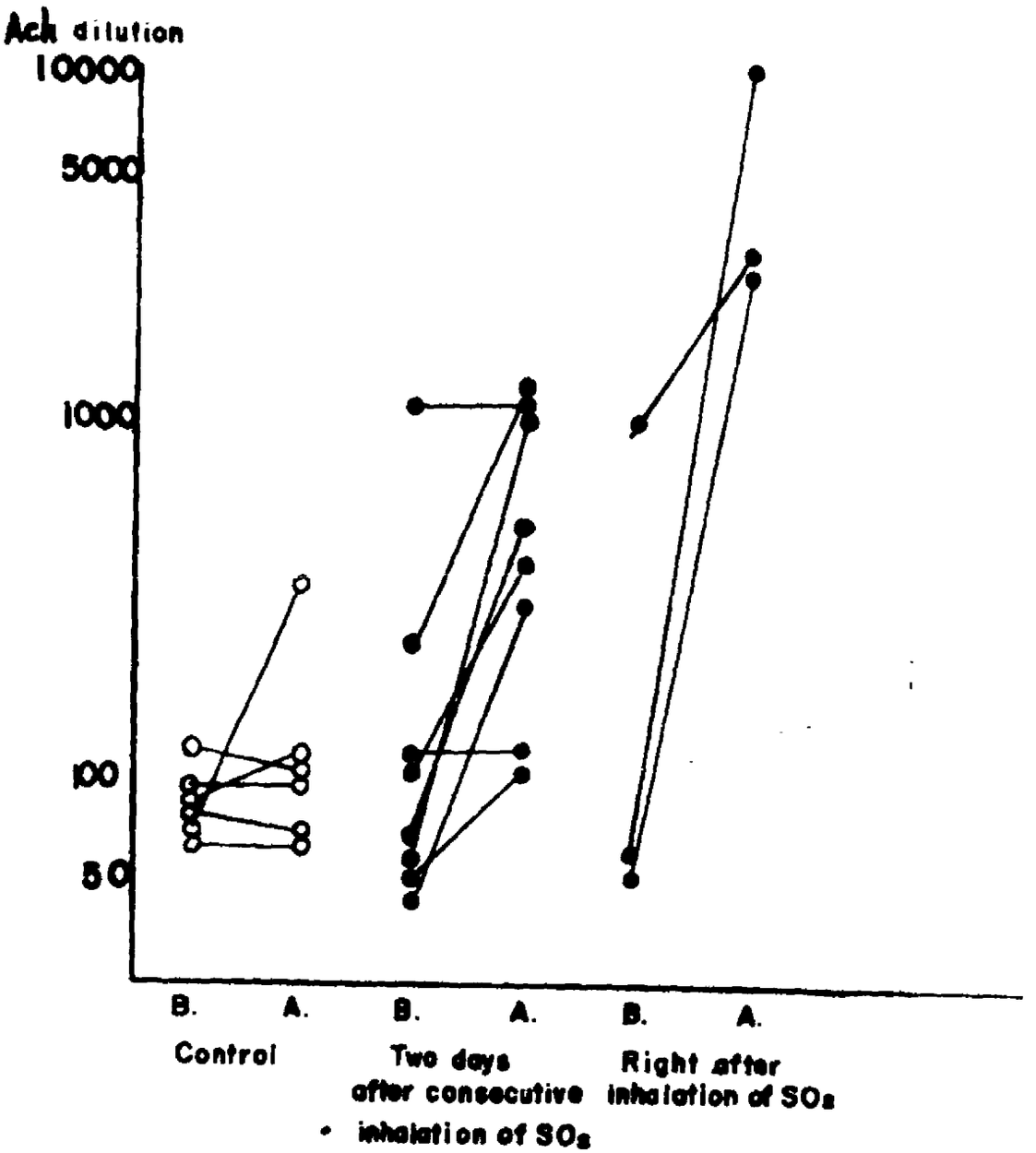

Fig. 5. Sensitivity to Acetylcholine in Guinea Pigs after Inhalation of SO_2.

TABLE 1. Number of Subjects, Average Age, Incidence of Smoking, Average Smoking Year in Each Group.

Co.	Area	Group	No. of Subject	Average Age	Incidence of Smoking	Average Smoking Year
Oil Co.	Niigata	Nat.	473	34.9 ± 11.6	328 (69.3%)	2[illegible] ± 16[illegible].4
	T-Y Area	Nat.	655	26.2 ± [illegible].8	3[illegible]4 ([illegible]7.2%)	132.6 ± 1[illegible].[illegible]
		1	242	23.[illegible] ± 6.3	1[illegible] (64.1%)	75.2 ± [illegible]3.4
		2	236	28.8 ± 7.4	176 (74.6%)	142.3 ± 1[illegible].[illegible]
		3	330	36.5 ± 11.7	235 (71.1%)	279.7 ± 218.4
Casting Co.		Nat.	238	33.2 ± 10.2	183 (77.0%)	2[illegible]4.4 ± [illegible]48.2
		1	180	24.0 ± 7.0	99 (55.0%)	94.[illegible] ± 121.8
		2	170	29.9 ± 13.8	122 (71.8%)	142.5 ± 1[illegible].4
		3	301	39.9 ± 11.0	248 (82.4%)	265.[illegible] ± 164.[illegible]

Nat. : Native group

Group 1, 2 and 3 : Non-native group of T-Y area

1 : Living in T-Y area less than [illegible]

2 : Living in T-Y area between [illegible]

3 : Living in T-Y area more than 1[illegible] years

TABLE 2. Respiratory Symptoms and Smoking in Each Group.

Increased Sputum Production

Co.	Area	Group	Age in Years: below 25 S	below 25 NS	26 - 35 S	26 - 35 NS	36 - 45 S	36 - 45 NS	above 46 S	above 46 NS	Total S	Total NS	Total
Oil Co.	Niigata	Nat.	7 (21.7%)	3 (3.5%)	6 (8.3%)	4 (14.8%)	12 (10.8%)	0 -	14 (15.2%)	1 (7.7%)	39 (12.7%)	8 (5.1%)	47 (9.7%)
	T-Y Area	Nat.	30 (15.4%)	13 (6.6%)	21 (18.2%)	6 (10.9%)	16 (27.6%)	2 (15.4%)	6 (26.1%)	0 -	73 (19.5%)	21 (7.7%)	94 (14.8%)
		Non-nat.	2 (11.2%)	8 (5.4%)	36 (16.8%)	5 (9.4%)	16 (18.4%)	2 (10.5%)	20 (22.2%)	0 -	93 (16.3%)	15 (6.1%)	107 (13.4%)
Casting Co.		Nat.	2 (25.7%)	2 (9.1%)	9 (13.6%)	2 (12.5%)	5 (12.8%)	0 -	8 (28.5%)	0 -	30 (16.9%)	5 (10.9%)	35 (16.4%)
		Non-nat.	2 (22.1%)	9 (12.9%)	32 (21.0%)	7 (25.9%)	11 (11.6%)	1 (5.6%)	14 (18.2%)	1 (4.5%)	77 (18.6%)	18 (11.2%)	95 (16.7%)

Chronic Coughing

Oil Co.	Niigata	Nat.	-	-	5 (4.2%)	2 (7.2%)	6 (5.4%)	2 (3.3%)	8 (8.7%)	0 -	17 (5.5%)	4 (3.8%)	21 (14.4%)
	T-Y Area	Nat.	4 (3.2%)	2 (1.0%)	7 (6.0%)	2 (5.6%)	12 (20.7%)	2 (15.4%)	2 (8.7%)	0 -	25 (6.7%)	6 (2.2%)	31 (4.4%)
		Non-nat.	6 (5.4%)	6 (4.0%)	17 (8.0%)	3 (5.7%)	5 (5.8%)	2 (10.0%)	7 (7.8%)	0 -	35 (6.1%)	11 (4.5%)	46 (5.6%)
Casting Co.		Nat.	2 (5.7%)	0 -	4 (6.1%)	5 (18.8%)	2 (5.1%)	0 -	2 (7.1%)	0 -	10 (5.6%)	3 (6.5%)	13 (6.2%)
		Non-nat.	[illegible]	[illegible]	15 [illegible]	5 (13.5%)	8 (8.5%)	0 -	9 (11.7%)	0 -	38 (9.2%)	10 (7.3%)	48 (7.8%)

[illegible] Irritation

[illegible]	[illegible]	Nat.	5 (12.5%)	2 (6.3%)	2 (4.7%)	2 (7.4%)	3 (5.2%)	2 (6.7%)	7 (8.7%)	1 (7.7%)	27 (7.4%)	7 (4.5%)	34 (7.2%)
[illegible]	T-Y Area	Nat.	17 (8.9%)	5 (5.0%)	15 (8.6%)	4 (10.4%)	8 (13.8%)	1 (7.7%)	1 (4.3%)	0 -	41 (10.1%)	15 (5.9%)	56 (8.3%)
		Non-nat.	17 [illegible]	3 (3.3%)	14 (9.4%)	6 (11.5%)	10 (11.5%)	1 (5.0%)	7 (7.8%)	0 -	46 (8.6%)	15 (6.1%)	61 (7.7%)
[illegible]		Nat.	[illegible]	[illegible]	1 (14.5%)	[illegible]	4 (10.3%)	1 (33.3%)	2 (7.1%)	0 -	25 (12.9%)	2 (4.3%)	25 (11.7%)
[illegible]		Non-nat.	1 (16.7%)	1 (7.1%)	25 (15.7%)	4 (14.[illegible]%)	12 (10.5%)	0 -	12 (15.6%)	2 (9.1%)	66 (14.7%)	11 (8.8%)	77 (12.4%)

TABLE 2. Continued.

Shortness of Breath

Co.	Area	Group	Age in Years: below 25 S	below 25 NS	26 - 35 S	26 - 35 NS	36 - 45 S	36 - 45 NS	above 46 S	above 46 NS	Total S	Total NS	Total
Oil Co.	Niigata	Nat.	1 (5.1%)	1 (1.2%)	1 (1.4%)	0 -	1 (1.8%)	1 (3.3%)	1 (1.1%)	0 -	4 (1.6%)	2 (1.3%)	6 (1.4%)
	T-Y Area	Nat.	3 (1.6%)	2 (0.5%)	1 (0.9%)	2 ([illegible])	2 (3.4%)	1 (7.7%)	0 -	0 -	6 (1.6%)	5 (0.7%)	11 (1.2%)
		Non-nat.	4 (3.4%)	0 -	5 (1.4%)	0 -	2 (2.3%)	1 (5.0%)	2 (2.2%)	0 -	13 (2.3%)	1 (0.4%)	14 (1.7%)
Casting Co.		Nat.	1 (2.9%)	0 -	2 (3.0%)	1 (6.3%)	0 -	0 -	2 (7.1%)	0 -	5 (2.8%)	1 (2.2%)	6 (2.8%)
		Non-nat.	2 (5.3%)	3 (4.3%)	7 (4.6%)	2 (7.4%)	3 (5.2%)	2 (11.1%)	6 (7.8%)	0 -	18 (4.6%)	7 (5.1%)	25 (4.7%)

Nat. : Native

Non-nat. : Non-native

S : Subjects with smoking habit

NS : Subjects without smoking habit

Table 5. Respiratory Symptoms and Allergic Constitution in Each Group.

Increased Sputum Production

Area	Group	Age in Years: below 25 A	below 25 NA	26 - 35 A	26 - 35 NA	36 - 45 A	36 - 45 NA	above 46 A	above 46 NA	Total A	Total NA	Total
Oil Co.	Niigata Nat.	5 (17.8%)	5 (5.4%)	5 (14.7%)	5 (5.9%)	7 (19.4%)	5 (5.5%)	6 (20.7%)	9 (11.4%)	23 (13.1%)	24 (6.9%)	47 (9.7%)
	T-Y Area Nat.	17 (16.7%)	26 (8.1%)	14 (22.0%)	13 (11.4%)	12 (52.2%)	6 (12.8%)	2 (20.0%)	4 (17.4%)	45 (22.6%)	49 (9.7%)	94 (14.8%)
	T-Y Area Non-nat.	9 (11.0%)	19 (8.4%)	18 (19.3%)	23 (12.6%)	8 (23.1%)	10 (15.2%)	10 (51.0%)	10 (11.4%)	45 (15.6%)	62 (10.9%)	107 (13.4%)
Casting Co.	Nat.	3 (21.4%)	8 (17.0%)	3 (12.5%)	8 (13.8%)	2 (15.4%)	3 (9.1%)	4 (57.1%)	4 (13.3%)	12 (20.7%)	23 (13.7%)	35 (16.4%)
	Non-nat.	6 (15.0%)	23 (17.2%)	13 (30.2%)	26 (15.4%)	6 (18.7%)	6 (6.3%)	4 (16.6%)	11 (10.0%)	29 (20.0%)	66 (13.0%)	95 (16.7%)
Chronic Coughing												
Oil Co.	Niigata Nat.	0 -	0 -	2 (5.9%)	3 (3.6%)	4 (11.1%)	4 (4.4%)	5 (17.2%)	3 (3.8%)	11 (8.7%)	10 (2.9%)	21 (4.4%)
	T-Y Area Nat.	3 (2.9%)	3 (0.9%)	7 (10.9%)	2 (1.8%)	10 (45.5%)	4 (8.5%)	1 (10.0%)	1 (4.4%)	21 (10.6%)	10 (2.0%)	31 (4.4%)
	T-Y Area Non-nat.	7 (7.5%)	5 (1.8%)	12 (10.8%)	8 (5.4%)	4 (15.4%)	3 (6.3%)	4 (10.3%)	3 (3.8%)	27 (10.0%)	19 (3.8%)	46 (5.6%)
Casting Co.	Nat.	1 (7.1%)	1 (2.2%)	4 (16.7%)	3 (5.2%)	1 (7.7%)	1 (3.0%)	2 (28.6%)	0 -	8 (13.8%)	5 (3.0%)	13 (6.2%)
	Non-nat.	3 (6.5%)	8 (5.3%)	9 (20.9%)	11 (6.5%)	3 (9.4%)	3 (5.3%)	3 (12.5%)	6 (5.5%)	18 (12.4%)	30 ([illegible])	48 ([illegible])
Throat Irritation												
Oil Co.	Niigata Nat.	2 (7.1%)	3 (3.2%)	2 (5.9%)	3 (5.3%)	4 (11.1%)	3 (7.7%)	3 (10.3%)	5 (6.5%)	11 (8.7%)	23 (6.6%)	34 (7.2%)
	T-Y Area Nat.	10 (9.8%)	12 (3.7%)	13 (20.1%)	11 (9.6%)	5 (21.7%)	4 (8.5%)	1 (10.0%)	0 -	29 (14.6%)	27 (5.3%)	56 (8.3%)
	T-Y Area Non-nat.	7 (8.5%)	16 (7.1%)	13 (15.7%)	7 (4.2%)	3 (11.5%)	8 (10.3%)	4 (15.7%)	3 (5.8%)	27 (12.5%)	54 (6.0%)	81 (7.7%)
Casting Co.	Nat.	1 (7.1%)	7 (14.9%)	4 (16.7%)	7 (12.1%)	3 (23.1%)	2 (6.1%)	1 (14.3%)	0 -	9 (15.5%)	16 ([illegible])	25 (11.7%)
	Non-nat.	6 (15.0%)	16 (11.9%)	11 (25.5%)	18 (10.7%)	6 (18.8%)	6 (6.3%)	2 (8.4%)	12 (11.0%)	25 (17.3%)	[illegible] (11.2%)	77 (12.4%)

TABLE 5. Continued

Shortness of Breath

Co.	Area	Group	Age in Years: below 25 A	below 25 NA	26 - 35 A	26 - 35 NA	36 - 45 A	36 - 45 NA	above 46 A	above 46 NA	Total A	Total NA	Total
Oil Co.	Niigata	Nat.	2 (7.1%)	0 -	1 (1.2%)	0 -	0 -	2 (2.2)	0 -	1 (4.5)	3 (2.4)	3 (0.9)	6 (1.4)
	T-Y Area	Nat.	2 (2.0%)	3 (0.9%)	1 (1.6%)	2 (1.8%)	3 (15.0)	0 -	0 -	0 -	6 (3.0%)	5 (1.0%)	11 (1.5%)
		Non-nat.	0 -	4 (1.7%)	4 (4.8%)	1 (0.7%)	3 (11.5%)	0 -	2 (6.8)	0 -	9 (5.9)	5 (0.9%)	14 (1.7%)
Casting Co.		Nat.	1 (7.1%)	0 -	1 (4.2%)	2 (3.4%)	0 -	0 -	2 (28.6)	0 -	4 (7.1)	2 (1.2%)	6 (2.8%)
		Non-nat.	1 (2.2%)	4 (2.9%)	3 (2.3%)	6 (3.6%)	4 (12.5%)	1 (1.1%)	2 (8.3%)	4 (5.6)	10 (6.2)	15 (2.8)	25 (4.7%)

Nat. : Native

Non-nat. : Non-native

A : Subjects with allergic constitution

N : Non-allergic subjects

TABLE 4. Mean Value of $\frac{VC}{\text{pred. } VC} \times 100$ in Each Group.

Co.	Area	Group	below 20	21 - 25	26 - 30	31 - 35	36 - 40	41 - 45	46 - 50	above 51
Oil Co.	Niigata	Nat.	100.41 ± 12.18	96.09 ± 11.29	97.47 ± 10.00	98.06 ± 12.65	99.25 ± 11.52	102.89 ± 14.12	99.50 ± 12.30	100.57 ± 11.51
	T-Y Area	Nat.	98.09 ± 10.06	94.59 ± 9.73	97.79 ± 11.53	94.68 ± 10.95	97.88 ± 11.17	94.66 ± 9.96	89.56 ± 13.94	93.23 ± 13.15
		1	96.91 ± 10.73	97.32 ± 10.27	99.29 ± 8.50	101.95 ± 4.44	98.25 ± 7.94	88.43 ± 13.16	86.18 ± 13.56	103.60 ± 0.00
		2	99.75 ± 8.49	97.15 ± 7.72	98.61 ± 10.42	99.37 ± 9.86	100.51 ± 11.86	98.05 ± 9.61	96.90 ± 10.98	90.17 ± 19.90
		3	95.69 ± 9.73	92.24 ± 9.21	95.27 ± 10.42	95.34 ± 11.71	96.01 ± 12.77	9[illegible].13 ± 11.26	96.15 ± 11.67	98.07 ± 12.00
Casting Co.		Nat.	90.82 ± 11.45	91.02 ± 7.90	88.88 ± 10.74	89.57 ± 11.60	86.86 ± 8.86	88.97 ± 13.81	[illegible].39 ± 17.09	93.25 ± 11.02
		1	96.60 ± 10.75	94.07 ± 10.86	93.50 ± 10.36	96.53 ± 10.15	85.77 ± 8.77	97.63 ± 5.66	9[illegible].0	89.95 ± 12.49
		2	97.78 ± 11.71	88.38 ± 8.94	92.46 ± 10.08	98.26 ± 11.01	90.06 ± 12.62	85.05 ± 1[illegible].09	1[illegible].1[illegible] ± [illegible].0	80.90
		3	99.20 ± 2.72	9[illegible].78 ± 25.39	94.64 ± 11.03	91.75 ± 9.34	90.54 ± 15.91	89.1[illegible] ± 14.02	[illegible].[illegible] ± 1[illegible].95	90.35 ± 15.89

: Statistically significant difference by $\hat{t}$-test

Nat. : Native group

Group 1, 2 and 3 : Non-native group of T-Y area

1 : Living in T-Y area less than 5 years

2 : Living in T-Y area between 5 and 10 years

3 : Living in T-Y area more than 10 years

TABLE 5. $\frac{FEV_1}{VC} \times 100$ in Each Group.

Below Age of 25

Co.	Area	Group	$\frac{FEV_1}{VC} \times 100$ below65	66-70	71-75	76-80	81-85	86-90	91-95	96-100	Total
Oil Co.	Niigata	Nat.			1	3	19	44	34	21	122
	T-Y Area	Nat.		2	2	4	62	120	143	71	404
		1			3	2	21	61	67	24	178
		2					7	31	25	10	73
		3		1		1	7	17	34	6	66
Casting Co.		Nat.			1	2	4	22	15	15	59
		1		1	2	4	16	37	29	14	103
		2			1	3	5	16	19	5	49
		3					1	5	3	1	10

Between Age of 26 - 35

Oil Co.	Niigata	Nat.				5	45	38	23	8	119
	T-Y Area	Nat.		1	3	6	42	57	44	22	175
		1			1	4	12	13	11	4	45
		2	1		2	5	33	50	22	14	127
		3		1	2	4	18	36	21	10	92
Casting Co.		Nat.	1			4	18	32	25	7	85
		1		1		3	8	16	8	3	39
		2			1	5	19	20	17	3	65
		3		1	2	6	11	40	15	2	77

TABLE 5. Continue.

Between Age of 36 - 45

Co.	Area	Group	$\frac{FEV_1}{VC}$ x 100								Total
			Below65	66-70	71-75	76-80	81-85	86-90	91-95	96-100	
Oil Co.	Niigata	Nat.	1	3	7	12	61	26	21	1	132
	T-Y Area	Nat.			4	3	31	22	6	1	67
		1					5	2	2	1	10
		2				2	9	7	4	2	24
		3			1	7	24	30	13	3	78
Casting Co.		Nat.		1	2	7	9	15	8	2	44
		1			1	1	2	2			6
		2	1			1	5	8	4	2	21
		3			3	8	16	33	13	7	80

Above Age of 46

Oil Co.	Niigata	Nat.	2	2	2	13	51	24	8	1	103
	T-Y Area	Nat.	1	3	7	9	6	2			28
		1		1			1	3			5
		2	1		1	2	2	1	1		8
		3	1		4	11	47	25	9	2	99
" Casting Co.		Nat.		2	4	8	8	7	4	1	34
		1	1						2		3
		2			1	1	1	1	1		5
		3		2	7	7	23	25	13	4	81

Nat. : Native group

Group 1, 2 and 3 : Non-native group of T-Y area

1 : Living in T-Y area less than 5 years

2 : Living in T-Y area between 5 and 10 years

3 : Living in T-Y area more than 10 years

TABLE 6. Relation between $\frac{FEV_1}{FEV_0} \times 100$ and Respiratory Symptoms from the Point of Smoking Habit and Allergic Constitution.

$\frac{FEV_1}{FEV_0} \times 100$	Respiratory Symptoms															
	Increased Sputum Production				Chronic Coughing				Throat Irritation				Shortness of Breath			
	S	NS	A	NA	S	NS	A	NA	S	NS	A	NA	S	NS	A	NA
More than 80%	171	55	91	131	61	17	42	34	131	38	65	99	21	10	13	15
	(14.4%)	(5.1%)	(18.9%)	(10.2%)	(5.1%)	(2.8%)	(8.7%)	(2.7%)	(11.0%)	(6.3%)	(13.5%)	(7.5%)	(1.7%)	(1.6%)	(2.7%)	(1.1%)
Less than 80%	25	0	16	18	20	6	8	13	16	0	7	9	7	0	2	4
	(15.7%)	-	(38.0%)	(20.4%)	(12.5%)	(16.2%)	(19.0%)	(14.7%)	(10.0%)	-	(16.6%)	(10.2%)	(4.4%)	-	(4.7%)	(4.5%)

S : Subjects with smoking habit

NS : Subjects without smoking

A : Subjects with allergic consitution

NA : Non-allergic subjects

TABLE 8. Place of Onset of Asthma in 237 Asthmatic Patients in Our Clinic.

Birthplace	Place of Onset of Asthma	Number of Cases
T-Y area	T-Y area	76
T-Y area	Rural area	9
Rural area	Rural area	89
Rural area	T-Y area	38
Not Specified	T-Y area	38
Not Specified	Rural area	10

TABLE 9. Pulmonary Function Studies in 3 Cases Reported.

	Case 1	Case 2	Case 3
Age	30	30	19
Sex	Male	Male	Female
Height	168 cm	162 cm	155 cm
V C (ℓ)	4.06	3.38	2.79
FEV_1	50 %	66 %	60 %
TLC (ℓ)	5.98	6.92	4.38
R V (ℓ)	1.92	2.52	1.73
FRC (ℓ)	3.48	4.08	2.71
MBC (ℓ)	69	54.4	44.7
D_{LCO}	28.3	41.5	42.3